REMARKS

Claims 1-9 are pending. No claim is herewith added or deleted. Thus, with the entry of this amendment, claims 1-9 will remain active. Claims 3 and 5 are amended. No new matter is added with the amendment.

I. Rejections under 35 USC § 112

The Examiner has rejected claims 3 and 5 for lack of enablement on account of the recitation of "preventing." Applicants respectfully traverse this rejection. However, in order to advance prosecution, applicants have amended claims 3 and 5 to delete "preventing." Thus, this rejection is moot and withdrawal thereof is respectfully requested.

II. Rejections under 35 USC § 102

The Examiner has rejected claims 1-5 under 35 USC § 102(b) as being anticipated by Suh, WO 03/007947 ("Suh"). According to the Examiner, Suh teaches salts of N-Hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)-phenoxy] pentoxy}-benzamidine and that salts of methanesulfonic acid are taught as being preferred at page 4, lines 1-13. The Examiner gives no weight to the recitation of the uses recited in claims 3-5.

As for claim 2, directed to a method of preparing N-Hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)-phenoxy] pentoxy}-benzamidine 2 methanesulfonic acid salt, the Examiner states that because methanesulfonic acid salt of the compound are disclosed, it is inherent that to form N-Hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)-phenoxy] pentoxy}-benzamidine 2 methanesulfonic acid salt, a reaction inherently occurs between N-Hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)-phenoxy] pentoxy}-benzamidine and a methane sulfonic acid.

Applicants respectfully traverse these rejections. Contrary to the Examiner's conclusion, Suh does not teach the salt that applicants are claiming, namely, N-Hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)-phenoxy] pentoxy}-benzamidine

2 methanesulfonic acid salt (emphasis added). That is, Suh does not teach a 2 methane sulfonic acid salt of N-Hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)-phenoxy] pentoxy}-benzamidine. A "2 methane sulfonic acid salt" means that two methanesulfonic acid molecules are bonded to one free base compound to form a salt.

Suh describes N-Hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)-phenoxy] pentoxy}-benzamidine (DW 1350). At page 4, lines 5-13, Suh provides a "laundry list" of salts. Although Suh exemplifies methanesulfonic acid as an organic acid, it does not teach a "2 methanesulfonic acid." It is known that a chemical compound can be in the form of a salt, and that salt molecules can be bonded to one free base compound (compound molecule: salt molecule) in many different ratios. Examples of such ratios are 1:1, 1:2, 1:3, 2:1, 3:1, 4:1, etc. Suh's teachings with regard to salts are generic and do not direct one to a particular ratio. It does not explicitly or implicitly teach the species, *i.e.* a 2 methanesulfonic acid salt, which is recited in the rejected claims. At page 6, under "preparation of specimen," compound DW1350 is mentioned. This is free-base N-Hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)-phenoxy] pentoxy}-benzamidine. It is not a salt. Thus, there is not an inherent teaching of the claimed salt. In view of these deficiencies in Suh, applicants respectfully request the Examiner to withdraw the lack of novelty rejection over Suh.

Further, applicants also point out that Suh nowhere teaches pharmaceutical compositions comprising amounts of N-Hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)-phenoxy] pentoxy}-benzamidine 2 methanesulfonic acid salt effective for treating osteoporosis, bone fractures or allergic inflammatory diseases, as recited in amended claims 3-5. Accordingly, applicants respectfully request the Examiner to withdraw the rejection under 35 USC § 102.

III. Rejections under 35 USC § 103

The Examiner rejects claims 6-9 under 35 USC § 103 as being obvious over Suh, as applied to claims 1 and 3-5, in view of Hirano *et al.*, US Patent Application No. 2004/0019045 ("Hirano").

According to the Examiner, Suh teaches methane sulfonic acid salts of N-Hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)-phenoxy] pentoxy}-benzamidine, and compositions administered orally, at page 4, line 31 to page 5, line 3. The Examiner admits that excipients calcium carbonate and sodium croscarmellow are not explicitly taught. The Examiner cites Hirano for teaching pharmaceutical compositions for treating bone loss, osteoporosis and for promoting bone formation that include calcium carbonate and croscarmellow. The Examiner concludes that one would have been motivated to include calcium carbonate and croscarmellow because Hirano teaches that such excipients are commonly present in pharmaceutical compositions for oral administration and because Hirano's compositions are for the same use conditions as applicants. Applicants respectfully traverse this rejection.

First, applicants stress that Suh does not teach N-Hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)-phenoxy] pentoxy}-benzamidine 2 methanesulfonic acid salt. Nothing in Hirano would cure this deficiency. Thus, one could not combine Suh and Hirano to arrive at the claimed invention, and the Examiner has not set forth a *prima facie* case of obviousness.

Secondly, but not as a concession that the Examiner's obviousness rejection has merit, applicants point out that the 2 methane sulfonic acid salt of N-Hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)-phenoxy] pentoxy}-benzamidine) has properties that would have been unexpected. In the present application, at page 15, in Example 1, applicants teach the preparation of the 2 methane sulfonic acid salt of N-Hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)-phenoxy] pentoxy}-benzamidine, which is designated DW 1350. At page 16, under Comparative Example 1, applicants show the preparation of 1 methane sulfonic acid salt of N-Hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)-phenoxy] pentoxy}-benzamidine. Examples 2 and 4 provide data

comparing the two different salts. Example 2 shows that 2 methane sulfonic acid salt of N-Hydroxy-4-{5-[4-(5-isopropyl-2-methyl-1,3-thiazol-4-yl)-phenoxy] pentoxy}-benzamidine exhibited solubility about 3-fold higher at pH 4.0 and about 9-fold higher in distilled water in comparison to 1 methane sulfonic acid salt of DW 1350, as well as to the free base of DW 1350. Table 3 at page 18 of the present application summarizes these data and an annotated (*) version, indicating the increase in solubility, is reproduced below:

[Table 3]

Solvent	Free base	Used salt	
		1 methanesulfonic acid salt	2 methanesulfonic acid salt
Distilled water	3.48	414.34	3,535.33 ***(1015 times better than Free base and 8.5 times better than 1 MSA)**
pH 1.2	950.87	1,092.98	1,686.71 ***(1.7 times better than Free base and 1.5 times better than 1 MSA)**
pH 4.0	-	0.99	3.00 ***(3.0 times better than 1 MSA)**

Applicants also have shown that the 2 methane sulfonic acid salt of DW 1350 has significantly better bioavailability than the 1 methane sulfonic acid salt of DW 1350. Example 4 describes the pharmacokinetic evaluation of 2 methane sulfonic acid salt of DW 1350 and provides comparisons with 1 methane sulfonic acid salt of DW 1350. These data are summarized in Table 5 at page 21 of the present application and show that in distilled water, the 2 methane sulfonic acid salt of DW 1350 exhibited bioavailability of 46% or higher, relative to the 1 methane sulfonic acid salt of DW 1350. An annotated (*) copy of this table, indicating the increase in bioavailability, is reproduced below.

[Table 5]

Solvent	Free base	Used salt	
		1 methanesulfonic acid salt	2 methanesulfonic acid salt
Cmax (μg/ml)	1.09±0.17	1.40±0.11	1.67±0.32 ***(1.5 times better than Free base and 1.2 times better than 1 MSA)**
AUC (μg/ml)	5.31±0.49	7.01±0.60	10.28±0.80 ***(1.9 time better than Free base and 1.5 times better than 1 MSA)**

Again, applicants strongly disagree that the invention of rejected claims 6-9 would have been obvious over Suh alone, or in combination with Hirano. Suh fails to teach the claimed salt of DW 1350 and Hirano, which is not concerned with DW 1350, does not cure this deficiency regardless of what it teaches about formulations for other compounds. Additionally, applicants argue that the 2 methane sulfonic acid salt of DW 1350 would not have been obvious over a generic description of methane sulfonic acid salts of DW 1350 in Suh. Applicants have shown that the 2 methane sulfonic acid salt of DW 1350 has surprising benefits over the 1 methane sulfonic acid salt of DW 1350, as discussed above.

In view of these arguments, applicants respectfully request the Examiner to withdraw the rejection of claims 6-9 over Suh and Hirano.

IV. Double Patenting Rejections

The Examiner has provisionally rejected claims 1 and 3-9 for obviousness type double patenting over claims 1-12 of copending application no. 11/577,469. Applicants respectfully traverse this provisional rejection but will fully respond upon a receipt of an indication of allowable subject matter.

CONCLUSION

In the event that additional fees are necessary in view of this amendment or the Examiner's Amendment, then such fees are hereby authorized to be charged to our Deposit Account No. 01-2300 referencing docket number 027707.00031.

Respectfully submitted,

January 22, 2010

Patricia D. Granados

Patricia D. Granados
Registration No. 33,683

Customer No. 004372
ARENT FOX LLP
1050 Connecticut Avenue, N.W.,
Suite 400
Washington, D.C. 20036-5339
Tel: (202) 857-6000
Fax: (202) 638-4810
PDG/knc